

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Therapeutically Active Bismuth Organic Compounds

I, ERNST ALBERT HERMANN FRIEDHEIM, of 333, West 52nd Street, New York City, United States of America, a Swiss citizen, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

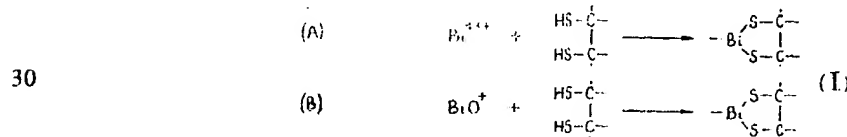
The present invention relates to the preparation of new compounds of relatively low toxicity obtainable by reacting bismuth-containing materials with dimercapto compounds of the type described hereinafter.

Accordingly, this invention consists in a bismuth compound containing at least one five-membered ring of the formula



The invention further consists in a process for preparing a bismuth compound as defined above, which comprises reacting ionizable metallic bismuth or a bismuth compound with an organic vicinal dimercapto compound in the presence of a liquid reaction medium.

I have found that when ionizable metallic bismuth or an organic or inorganic bismuth compound is reacted with a dithiol (dimercapto compound) of the type described hereinafter, new compounds are formed according to the following general reaction schemes:

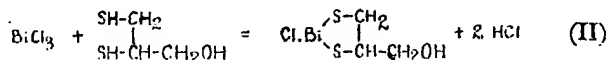


whereby the Bi atom becomes a part of a five-membered ring. The dimercapto group shown in the above reaction schemes represents a part of the radical of dimercapto compounds of the type described hereinafter, in which as shown above, the two —SH groups are attached to vicinal carbon atoms.

The above mentioned reaction takes place, for example, in an aqueous reaction medium or in organic liquids or solvents in which at least one of the two reaction components (bismuth compound and dithiol) is soluble. Whenever the dithiol is a liquid, it may be reacted

directly with the bismuth compound without the addition of a particular reaction medium, but the use of a liquid reaction medium is generally preferred. The reaction is widely independent from the pH. It takes place in a range extending from 4N HCl to 1N NaOH.

Depending on the reaction conditions, the third valency of bismuth in formula (I) may be saturated in various ways. If the reaction takes place in the presence of free halogen-hydrogen acids, then the third valency will be linked to halogen corresponding to the following example:



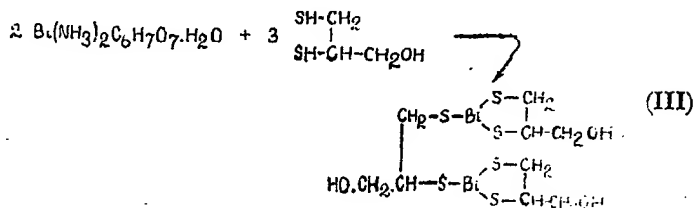
If the reaction is carried out in a neutral or slightly alkaline medium, in the presence of an excess of the dithiol, then two of the above

mentioned five-membered rings shown in scheme I are united or combined by a third dithiol radical in the following manner:

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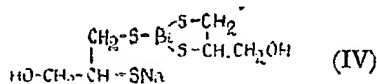
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Substances formed according to the above schemes I and II, in which all sulfur atoms present in the molecule are parts of a five-membered ring, are relatively stable. For example, the reaction product obtained according to scheme II is not decomposed by limited exposure to boiling water and dry heat up to 105° C.; the ring is not split to an appreciable degree in alkaline medium (1N NaOH) either. This is evidenced by the fact that tests of free —SH groups (sodium nitroprussiate, and reduction of Fehling solution) are negative.

In contrast to the before-mentioned substances formed according to schemes I and II, products formed according to the above scheme III are substantially more labile. For example, the reaction product according to scheme III is decomposed if heated to temperatures above 100° C. and the sulfur bismuth links which are not constituents of a pentatomic ring are partly split in 1N NaOH, as shown by the occurrence of positive reactions with the above mentioned —SH reagents. In this case yellow material goes into solution in NaOH and this material has probably the following structure:



Compounds of this type are likewise formed if the reaction between the bismuth compounds and the vicinal dithiol takes place in a strongly alkaline reaction medium.

All substances belonging to the types II, III and IV have a yellow color of various shades and intensities.

The reaction products of the type shown in the above schemes II and III, which are obtained from bismuth compounds and the dithiol shown in these schemes, have the following physical properties: They occur in the form of yellow powders and are insoluble in water, methyl alcohol, ethyl alcohol, acetone, ether, chloroform, glacial acetic acid, benzyl benzoate, carbon disulfide and propylene glycol. They are soluble in pyridine, quinoline, molten camphor (synthetic) and cold, concentrated sulfuric acid.

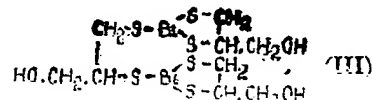
As starting material, in the reaction according to scheme I, any bismuth compound may

be used. As dithiol, I prefer the use of 2,3-dimercaptopropanol and 2,3 - dimercaptopropionic acid. However, other aliphatic or aromatic vicinal dithiols, i.e. dithiols in which the two —SH groups are attached to vicinal carbon atoms, may also be used. As the vicinal dithiols show a great affinity to bismuth ions, a reaction, which can be recognized by the occurrence of yellow compounds, occurs even in the case of bismuth compounds having small dissociation constants, such as bismuth salicylate, and tartrate, under suitable pH conditions.

The following description illustrates, by way of example and without limitation, some characteristic embodiments of my invention.

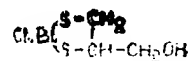
EXAMPLE 1.

1/10 mol. of bismuth sodium citrate, containing 1 atom Bi in the molecule, dissolved in ten parts of water, with the addition of sufficient aqueous ammonia to bring the reaction mixture to pH of 8 to 9, are run dropwise with mechanical stirring into a solution of 1/5 mol. of 2,3-dimercaptopropanol in a mixture of 8 parts of water and 8 parts of ethanol. A yellow precipitate is formed which is filtered off, washed with water and acetone and dried *in vacuo*. The ratio of bismuth to sulfur in this compound is 1:3, corresponding to the probable formula:



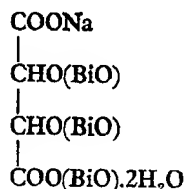
EXAMPLE 2.

12.4 g. of 2,3-dimercaptopropanol, dissolved in 50 ml. of methanol, are added dropwise with stirring to a solution of 23.3 g. of Bi₂O₃ in 100 ml. of concentrated HCl and 200 ml. of water. The temperature of the reaction mixture is 40° C. A yellow precipitate is formed, filtered off, washed with dilute HCl, acetone and ether and dried *in vacuo*. The bismuth:sulfur ratio in the compound thus obtained is 1:2, corresponding to the formula:

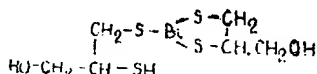


EXAMPLE 3.

29.2 g. (equivalent to .1 atom of Bi) of sodium tribismuthyl tartrate of the formula



- 5 dissolved in 1000 ml. of water, are run gradually with mechanical stirring in a nitrogen atmosphere into a mixture of 37.2 g. (.3 mol) of 2,3-dimercaptopropanol and 3000 ml. of N/1 NaOH. The reaction mixture turns yellow and some yellow precipitate is formed, which is removed by filtration. The clear yellow filtrate is reduced to dryness *in vacuo*. The resulting yellow product has a bismuth:sulfur ratio of 1:4, corresponding to the probable formula:



- 20 The sodium tribismuthyl tartrate was prepared (see W. F. von Oettingen and Y. Ishikawa, J. Am. Pharm. Assoc. 17, p. 124, 1928) by reacting $\text{Bi}(\text{NO}_3)_3$ in acetic acid with sodium tartrate, according to the method of Fabregue described in Pharm. et Chim. XXV (1922) p. 341. The product of this reaction is a compound of the formula $\text{C}_8\text{H}_4\text{O}_{15}\text{Bi}_3\text{Na}_2$; by dissolving this compound in water, in the presence of NaOH, and subsequent re-precipitation with alcohol, sodium tribismuthyl tartrate is formed.

EXAMPLE 4.

- 30 A solution of 149 g. (1.2 mol) of 2,3-dimercaptopropanol in 4 liters of ethanol is added gradually to a filtered solution of 181 g. (0.4 mol) of bismuth ammonium citrate (containing one atom Bi in the molecule) in 8 liters of warm water (30° C.). The resulting yellow precipitate is filtered off, washed with water and acetone and dried *in vacuo*. It forms a yellow powder which is insoluble in water, ethanol, acetone and chloroform and soluble in pyridine.

EXAMPLE 5.

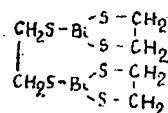
- 40 26.0 g. (1/10 mol) of freshly precipitated $\text{Bi}(\text{OH})_3$ are gradually introduced in finely dispersed condition under continuous vigorous stirring into a mixture of 24.8 g. of 2,3-dimercaptopropanol (2/10 mol) with 1 litre of N/1 aqueous sodium hydroxide solution and the stirring is continued for about 2 hours. A yellow substance corresponding to the above probable formula III is formed. This substance is separated from the aqueous liquid by filtration, washed with water and acetone and dried *in vacuo*.

EXAMPLE 6.

1/10 mol of bismuth sodium tartrate, containing 1 atom of bismuth in the molecule, is dissolved in the tenfold amount of water and this solution is run dropwise under mechanical stirring into a solution of 2/10 mol of 2,3-dimercaptopropionic acid and 3/10 mol NaOH in 1 liter of water. After stirring the reaction mixture for 20 minutes, it is acidified by the addition of acetic acid. The yellow substance formed is separated from the aqueous liquid by filtration, is washed free from impurities by water and acetone and is then dried under *vacuo*.

EXAMPLE 7.

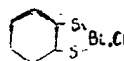
2/10 mol of 1,2-dithioethane is dissolved in ethyl alcohol and mixed under continuous vigorous stirring and gentle warming (40°—50° C.) with 1/10 mol of freshly precipitated $\text{Bi}(\text{OH})_3$ finely dispersed in 50% aqueous ethyl alcohol. The yellow compound has the probable formula:



It is washed with alcohol and acetone and dried *in vacuo*.

EXAMPLE 8.

1/10 mol of dithiocatechol dissolved in ethylalcohol is added in small portions to a solution of 1/10 mol of $\text{Bi}(\text{OH})_3$ in aqueous hydrochloric acid under vigorous stirring. The yellow precipitate formed is filtered off, washed with dilute aqueous hydrochloric acid, ice-cold acetone and ether and dried *in vacuo*. The product thus obtained has the probable formula:



EXAMPLE 9.

1/10 mol of bismuth ammonium citrate containing 1 atom Bi in the molecule, is dissolved in 10 parts of water and the solution is run dropwise with mechanical stirring into an aqueous solution of 2/10 mols of 2,3-dimercaptopropanol-glucoside. The pH of the reaction mixture should be adjusted by the addition of aqueous ammonia to 8—9. The yellow precipitate is filtered off, washed with water and acetone and dried *in vacuo*. The chemical structure of this product probably is analogous to that shown in formula III.

EXAMPLE 10.

8.3 g. of 2,3-dimercaptopropanol are added dropwise, with mechanical stirring, to 100 cc. of a solution of α -carboxyethyl- β -methyl nonoate containing 0.07 g. of bismuth metal per cc. A yellow precipitate is formed, which is separated

by filtration and washed with carbon disulfide and ether.

EXAMPLE 11.

6 g. of 2,3-dimercaptopropanol are added dropwise with stirring, to 100 cc. of a solution of bismuth thiolaurate in ethyl oleate, said solution containing 0.05 g. of bismuth metal per cc. A yellow precipitate is formed at room temperature instantaneously, which is separated by filtration, washed with acetone and ether and dried *in vacuo*.

As already mentioned above, the present invention is not limited to the above examples and may be carried out with numerous modifications with regard to the starting materials and their proportions used in the reaction, the nature of the reaction medium and the conditions under which the reaction takes place.

Thus, instead of the water-soluble bismuth compounds named in the above examples, other water soluble bismuth compounds, such as bismuth sodium potassium tartrate



basic bismuth potassium bismuthotartarate



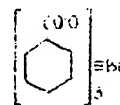
bismuth potassium tartrate $[\text{BiK}(\text{C}_4\text{H}_4\text{O}_6)_2]$, may be used substantially in the manner described in the above examples. Organometallic compounds containing bismuth radicals reacting with the two —SH groups of the dimercapto compound, such as



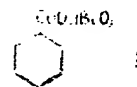
and compounds containing bismuth and arsenic, for example bismuth sodium *p*-aminophenylarsonate, may also be used in the present invention. But it is to be understood that in the above reaction schemes any bismuth compound may be employed. In these reaction schemes the bismuth ions, such as Bi^{+++} and/or BiO^+ may be provided, for instance, by any bismuth compound, such as salt, inner complex, which may be organic or inorganic, or any bismuth compound in which the bismuth is linked to the sulfur of an organic monomercaptide, which yields bismuth in a form which reacts with the dimercapto compound and, in particular, gives rise to the occurrence of bismuth ions or bismuthyl ions or bismuthate ions in the reaction medium. Even suspensions of only sparingly soluble bismuth compounds, such as bismuth subsalicylate, bismuth subgallate, bismuth subacetate, bismuth subbenzoate, or colloidal solutions of metallic bismuth, release under appropriate pH conditions sufficient bismuth ions to give rise to the reaction indicated in the above scheme (T), recognizable by the appearance of yellow colored products. The pH at which the reaction between the bismuth

compound and the dithiol is carried out depends primarily on the chemical properties of the bismuth compound. A reaction medium containing free acid, particularly hydrochloric acid, is used, if the addition of Cl into the bismuth atom is desired. If this is not the case, the reaction is preferably carried out in neutral or weakly alkaline solution.

In accordance with the above, for example the following substances are used as bismuth-containing starting materials in carrying out the present invention: metallic bismuth in finest subdivision; inorganic, neutral bismuth salts and hydroxides which split off or yield Bi^{+++} ions, such as $\text{Bi}(\text{NO}_3)_3$, BiCl_3 , $\text{Bi}(\text{OH})_3$; inorganic basic bismuth salts of the bismuthyl cation BiO^+ , for example $\text{BiO}(\text{NO}_3)$, BiOCl ; organic neutral bismuth salts, for example

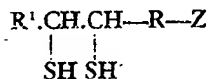


organic basic bismuth salts containing bismuth ions linked to oxygen, for example



organic inner complex products starting from Bi^{+++} or $(\text{BiO})^+$ and hydroxycarboxylic acids (tartaric acid, citric acid and salicylic acid).

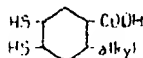
As shown by the above examples, 2,3-dimercaptopropanol is the preferred compound in carrying out my present invention. However, any other organic dithiol containing the —SH groups attached to vicinal carbon atoms may also be used. Particularly dimercapto compounds of the general formula:



in which R may be present or absent and stands for any aliphatic group containing up to 17 carbon atoms, and in which Z is always present and stands for H, —OH, —COOH, —COO-alkyl, —O-alkyl, CH_3 , or a glucose radical, and R^1 is H or alkyl, may be used in the preparation of bismuth-dimercapto derivatives substantially in the above described manner. The molecular proportions in which the dimercapto compounds are reacted with the bismuth compounds are illustrated in the above examples, but other proportions may also be used. The reaction products obtained in the process of the invention may also consist of the mixture of two or several dimercapto derivatives.

From the numerous aliphatic and aromatic

vicinal dimercapto compounds, which can be used as dithiols in my present invention, I prefer aliphatic dithiols of the following structure: $\text{HS}\cdot\text{CH}_2\text{—CH}_2\cdot\text{SH}$; $\text{HS}\cdot\text{CH}_2\text{CH}(\text{SH})\cdot\text{X}$, wherein X stands for one of the following radicals: $\text{—CH}_2\cdot\text{OH}$, —COOH , $\text{—CH}_2\cdot\text{O}\cdot\text{CH}_3$, $\text{—CH}_2\cdot\text{O}\cdot\text{glucose}$, $\text{—CH}_2\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$, $\text{—CH}_2\cdot\text{O}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$, $\text{—CH}_2\cdot\text{O}\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$; X may also stand for $\text{—CH}_2\cdot\text{O}\cdot\text{alkyl}$, $\text{—CH}_2\cdot\text{O}\cdot\text{acyl}$, $\text{—(CH}_2)_n\cdot\text{OH}$; $\text{—(CH}_2)_n\cdot\text{COOH}$; aromatic dithiols having the formula



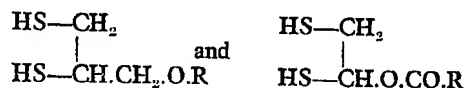
are likewise used. As additional specific examples of the vicinal dithiols, the following are mentioned: 2,3-dimercaptopropyl acetate; 2,3-dimercaptopropyl propionate; 2,3-dimercaptopropyl butyrate; 2,3-dimercaptopropyl methyl ether; 2,3-dimercaptopropyl ethyl ether; 2,3-dimercaptopropyl isopropyl ether; 2,3-dimercaptopropyl butyl ether; 2,3-dimercaptopropyl urea; 2,3-dimercaptopropyl urethane; 2,3-dimercaptopropyl glucoside; 2,3-dimercaptopropyl dodecyl sulfide; 2,3-dimercaptopropylamine; 2,3-dimercaptopropyl chloride; 2,3-dimercaptopropionic acid; methyl 2,3-dimercaptopropionate; ammonium 2,3-dimercaptopropionate; 3,4-dimercaptotetrahydrothiophene-1-dioxide; N-phenylaminopropane-2,3-dithiol hydrochloride; 10,11-dimercaptoundecanoic acid; 1,2-dimercaptopropane; ethanedithiol-1,2; dithiocatechol and other aromatic ortho-dithiols; phenylethanedithiol-1,2; cyclohexanedithiol-1,2; octanedithiol-1,2; hexadecanedithiol-1,2; 3,4-dimercaptobutanol; diethanolaminomethyl dithioglycerol-1,2; methyl-glucaminomethyl dithioglycerol-1,2; bis-S-(acetamidomethyl) dithioglycerol-1,2; bis-S-(N-ethylacetamidomethyl) dithioglycerol-1,2; mono-S-(acetamidomethyl) dithioglycerol-1,2; butanedithiol-2,3; 2-methylpropanedithiol-1,2; glucose mercaptal of dithioglycerol-1,2.

As the medium in which the bismuth-dimercapto derivatives according to my invention are prepared, I prefer to use water or an aqueous liquid at pH ranging from 1—10, which, however, may contain organic solvents which preferably are miscible with water. However, other suitable liquids may also be used. For example, bismuth ascorbate is dissolved in a mixture of chlorobutanol, benzyl alcohol and glycerin, or basic bismuth camphocarboxylate is dissolved in methanol, and either of the solutions thus obtained is reacted with the dimercapto compound. Or the bismuth compound, such as colloidal $\text{Bi}(\text{OH})_3$, is suspended in olive oil and is then reacted for example with 2,3-dimercaptopropanol, which

may also be dissolved in a vegetable oil, such as peanut oil, olive oil or sesame oil, if desired. Oil-soluble bismuth compounds, such as, for example bismuth butylthiolaurate, may be reacted in vegetable oil solution with the dimercapto compound. An aqueous suspension of $\text{Bi}(\text{OH})_3$ may be reacted by shaking it with a solution of 2,3-dimercaptopropanol in a vegetable oil, such as mentioned above, or an alcoholic solution of the latter is shaken with $\text{Bi}(\text{OH})_3$. To the aqueous or other reaction medium, suitable admixtures, such as additions for the adjustment of the pH, may be added. It may not always be necessary to isolate the reaction product or products resulting from the process of the present invention. For example, a mixture of 2 mols of $\text{Bi}(\text{OH})_3$ and 3 mols of 2,3-dimercaptopropanol in a liquid medium, such as water, peanut oil, ethyl oleate, or methyl-acetamide may be useful for medicinal or veterinarian purposes.

The reaction between the bismuth compounds and the dimercapto compounds is preferably carried out at ordinary room temperature i.e. $15^\circ\text{—}25^\circ\text{C}$., but lower temperatures, for example 2°C . and moderately increased temperatures, for example $40^\circ\text{—}60^\circ\text{C}$. may also be used. According to the invention, the organic vicinal dimercapto compound is reacted in a liquid reaction medium with the ionizable bismuth compound in the ratio of about $\frac{1}{2}$ to 4 mols of the dimercapto compound for one atom of bismuth.

The properties of the new compounds embodying my present invention vary, depending on the nature of the dithiol used in their preparation. Thus, if instead of 2,3-dimercaptopropanol other vicinal dithiols containing hydrophilic groups, such as —COOH , or polyalcohol groups, such as hexose radicals, are used, then the solubility characteristics of the bismuth-dimercapto derivatives are changed, for example water-soluble compounds are formed. Fat-soluble or oil-soluble bismuth dimercapto compounds are derived from ethers or esters of dithiopropanol of the type



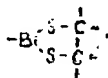
wherein R represents a fat-soluble or oil soluble radical.

The compounds pertaining to the present invention may be used for some of the same purposes as the known bismuth compounds, in particular the resorbable bismuth compounds, but have the advantage of considerably reduced relative toxicity in comparison to the latter. The products of my invention show a very satisfactory stability and are particularly useful in veterinarian and medical pharmaceuticals.

What I claim is:—

1. As a new compound, a bismuth com-

pound containing at least one five-membered ring of the formula



2. A bismuth compound as claimed in claim 1 formed as the reaction product of an organic vicinal dimercapto compound with ionizable metallic bismuth or a bismuth compound.
3. A bismuth compound as claimed in claim 2 in which the organic vicinal dimercapto compound is 2,3-dimercapto-propanol.
4. A bismuth compound as claimed in claim 2 in which the bismuth is linked to a sulfur atom of an organic monomercaptide radical.
5. A process for preparing a bismuth compound containing at least one five-membered ring of the formula



which comprises reacting ionizable metallic bismuth or a bismuth compound with an organic vicinal dimercapto compound in the presence of a liquid reaction medium.

6. A process as claimed in claim 5 in which an aromatic ortho-dithiol is used.

7. A process as claimed in claim 5 in which 2,3-dimercaptopropanol is used.

8. A process as claimed in claim 5 in which 2,3-dimercaptopropionic acid is used.

9. A process as claimed in claim 5 in which 2,3-dimercaptopropanol glucoside is used.

10. A process as claimed in claim 5 in which an inorganic bismuth salt is used.

11. A process as claimed in claim 5 in which bismuth hydroxide is used.

12. A process as claimed in claim 5 in which an organic bismuth compound containing bismuth linked to oxygen is used.

13. A process as claimed in claim 5 in which an organic bismuth compound containing arsenic is used.

14. A process as claimed in claim 5 in which an organic bismuth compound containing bismuth linked to carbon is used.

15. A process for producing new therapeutically active bismuth compounds substantially as described.

16. A new therapeutically active bismuth compound when produced substantially by a process as claimed in any of the preceding claims 5 to 14.

17. A new therapeutically active bismuth compound substantially as described.

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